REMARKS

Reconsideration of this application is respectfully requested. Applicants thank the Examiner for the courtesy of the interview on April 20, 2006.

Upon entry of the foregoing amendment, Claims 1, 2, 5-8 and 10-30 will remain pending in the application. Claims 2-3 and 9 have been canceled. Claim 30 has been added and Claims 1 and 5-7 have been amended. The support for the amended Claim 1 can be found, for example, on page 13, lines 7-9 and Figure 1. These changes do not introduce new matter, and their entry is respectfully requested.

In the Office Action of February 16, 2006, the Examiner set forth a number of grounds for rejection. These grounds are addressed individually and in detail below.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-9 and 15 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement for the reasons set forth on pages 3-8 of the outstanding Office Action. Specifically, the Examiner states that the specification, while being enabling for embodiments wherein the thrombomodulin coding sequence is operably linked to a promoter that mediates expression of TM in the mammal that mediates expression of TM in the mammal and wherein the thrombotic disease is atherosclerotic cardiovascular disease . . ." (See page 3 of the office action). In order to expedite prosecution, Applicants have amended independent Claim 1 to recite "A method for treating an atherosclerotic cardiovascular disease in a mammal, said method comprising: administering to said mammal at a site susceptible to a thrombus a therapeutically effective amount of a pharmaceutical composition comprising a gutless adenovirus vector, wherein said gutless adenovirus vector comprises a nucleotide sequence encoding human thrombomodulin having an amino acid sequence recited in SEQ ID NO:2 or its variant, a regulatory element operably linked to said nucleotide

sequence, and a stuffer sequence comprises a HPRT intron sequence, and wherein said human thrombomodulin or its variant is expressed in said mammal."

Accordingly, Applicants respectfully submit that the grounds for the rejection have been obviated. Withdrawal of the rejection to Claims 1-9 and 15 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1-9 and 15 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for reasons stated on pages 8-9 of the Office Action. Specifically, the Examiner alleges that none of the claims require expression of TM. In order to expedite prosecution, Applicants have amended claim 1 to indicate that TM is expression in the mammal. The Examiner also alleges that Claim 4 does not recite any positive process in which the "shuttle vector" is used. Applicants have canceled Claim 4. Accordingly, Applicants respectfully submit that the grounds for the rejection have been obviated. Withdrawal of the rejection to Claims 1-9 and 15 under 35 U.S.C. §112, second paragraph, is respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 1-3, 6-9 and 15 stand rejected under 35 U.S.C. 102(b) as being anticipated by Bach, et al. and Waugh, et al. for the reasons set forth on pages 9-10 of the Office Action. Claims 1 has been amended. Accordingly, Applicants respectfully traverse the rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. Of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).* The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed.*

Cir. 1989). There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic Research & Foundation v. Genentech Inc., 18 USPQ2d 1001, 1010 (Fed. Cir. 1991).*

In this case, the amended Claim 1 recites "A method for treating an atherosclerotic cardiovascular disease in a mammal, said method comprising: administering to said mammal . . . a therapeutically effective amount of a pharmaceutical composition comprising a gutless adenovirus vector, . . ." Neither Bach nor Waugh mentions gutless adenovirus vector. Accordingly, Bach and Waugh do not anticipate the present Claim 1 because they do not contain all of the elements of Claim 1. Applicants further submit that dependent claims 2, 6-8 and 15 are not anticipated by Bach and Waugh because they depend from Claim 1.

Thus, the grounds for this rejection have been obviated and withdrawal of the 35 U.S.C. 102(b) rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 103

Claims 1-4, 6-9 and 15 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 96/06933 to Bach, et al. (hereinafter "Bach") or Waugh and further in view of Vassalli, et al. (hereinafter "Vassalli") and Umana, et al. (hereinafter "Umana") for the reasons set forth on page 11 of the outstanding Office Action. Claims 4 have been canceled and Claim 1 has been amended. Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Moreover, when applying 35 U.S.C. § 103, the Examiner is required to adhere to the following tenets of patent law: (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (4) reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.,* 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

The amended independent Claim 1 directs to a method for **treating an atherosclerotic cardiovascular disease** in a mammal, said method comprising: administering to said mammal at a site susceptible to a thrombus a therapeutically effective amount of a pharmaceutical composition comprising a **gutless adenovirus** vector, wherein said gutless adenovirus vector comprises a nucleotide sequence **encoding human thrombomodulin** having an amino acid sequence recited in **SEQ ID NO:2** or its variant, a regulatory element operably linked to said nucleotide sequence, and a stuffer sequence comprises a **HPRT intron sequence**, and wherein said human thrombomodulin or its variant is expressed in said mammal.

As discussed above and admitted by the Examiner, Bach and Waugh do not teach the use of a gutless adenovirus. The Examiner alleges that Vassalli and Umana disclose the use of a gutless adenoviral vector and that "it would have been obvious to one of skill in the art to have utilized a gutless adenovirus in the methods of Bach or Waugh to take advantage of the longer expression times afforded by gutless adenoviral vectors as compared to the older adenoviral vectors used in Bach and Waugh." (Office Action, page 11). Nonetheless, neither Vassalli and Umana mention the **HPTR intro sequence** nor do they mention the treatment of an atherosclerotic cardiovascular disease nor do they mention human

thrombomodulin gene. Therefore, the Examiner is applying an improper "obvious to try" rationale in supporting of an obviousness rejection. As repeatedly asserted by the Examiner that "at the time the invention was made, gene therapy in general was highly unpredictable and still largely undeveloped art..." (See pages 5-8 of the outstanding office action.). Further in view of the Orkin, et al., Verma, et al. and Zuckerbraun, et al., which were cited by the Examiner for supporting the highly unpredictability of gene therapy, it is clear that the Examiner fails to address whether there is reasonable expectation of success, as required by MPEP 2143.02.

Further considering the fact that it is known in the art that gutless adenoviral vectors are difficult to construct and produce in large quantities. While several methods for producing gutless adenoviral vectors were known to one of ordinary skill in the art at the time of filing, only a limited number of gutless viral vectors were produced and tested in *in vitro* or *in vivo* settings. The major obstacle was that the construction of each gutless viral vector requires extensive experimentation. For example, the shuttle vector needs to contain a stuffer sequence of the proper size so that the total size of the DNA inserted into the gutless viral vector is within the packaging range of the adenovirus. After the construction of a shuttle vector, it is also difficult to produce and purify a gutless virus. In addition, the level of transgene expression is typically different among viral vectors carrying different transgenes. Therefore, each gutless vector needs to be specifically constructed and optimized for its intended use. For example, the apoptotic gene Bax results in premature cell death of the 293 packaging cell line and resulting in minimal yields of recombinant virus [Kagawa et al., *Gene Therapy*, 7:75-79 (2000)]. Accordingly, to achieve the present invention, a new vector with the specific gene of interest would need to be constructed and produced using a different method. The infection and expressing conditions would need to be reestablished through an enormous experimentation. At the time of the filing, one of ordinary skill in the art would

not successfully construct and produce a gutless adenoviral vector using the teaching of Vassalli and Umana and use the vector in Bach's or Waugh's method to practice the present Claim 1, e.g. treating an atherosclerotic cardiovascular disease in a mammal without undue experimentation. As pointed out by the CAFC in *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), "[T]he admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. . . In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* Accordingly, even if one of ordinary skill in the art were to combine Vassalli with Bach or Waugh, there would be no reasonable expectation of success, as required by MPEP 2143.02.

Accordingly, Applicants respectfully submit that Bach, Waugh, Vassalli and Umana individually or in combination, do not render Claims 1-2, 5, 7-9 and 15 obvious. These grounds for the rejection have been obviated and withdrawal of rejection under 35 U.S.C. § 103(a) is respectfully requested.

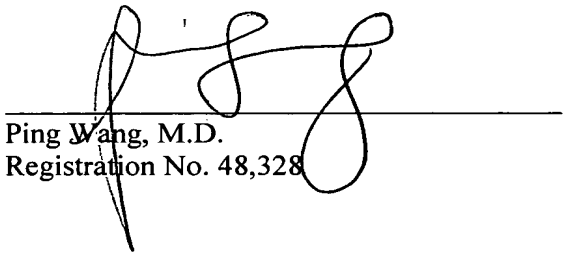
CONCLUSION

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to contact Ping Wang, M.D. (Reg. No. 48,328) at the telephone number listed below.

Respectfully submitted,

DLA PIPER RUDNICK GRAY CARY US LLP



Ping Wang, M.D.
Registration No. 48,328

1200 Nineteenth Street, N.W.
Washington, D.C. 20036-2412
Telephone No. 202.861.3900
Facsimile No. 202.223.2085